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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/087,714	02/28/2002	Daphna Havkin-Frenkel	DMCI-0099	7483

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EXAMINER	
COLLINS, CYNTHIA E	
ART UNIT	**PAPER NUMBER**
1638	

DATE MAILED: 05/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/087,714	HAVKIN-FRENKEL ET AL.	
	Examiner	Art Unit	
	Cynthia Collins	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-26,30 and 31* is/are pending in the application.

4a) Of the above claim(s) *26,30 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/13/02, 6/18/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group III, claims 16-25 directed to overproducing an enzyme associated with chain shortening of p-coumaric acid to p-hydroxybenzaldehyde, filed February 9, 2004, is acknowledged. Claims 1-15 and 27-29 are cancelled.

The traversal is with respect to claims 30-31 and on the ground(s) that rejoining claims 30 and 31 with the claims of Group III would not pose a serious additional search burden, as the first step of the method of Group III and the method of claims 30 and 31 are identical. This is not found persuasive because while the search of claims 30 and 31 may overlap with the search of Group III with respect to the first step of both methods, their searches are not coextensive of each other. In this particular instance, a search of claims 30 and 31 requires an additional search for techniques for inhibiting the production or activity of vanillyl alcohol dehydrogenase, which techniques are not required to practice the method of Group III. Accordingly claims 30 and 31 are withdrawn from consideration as being directed to non-elected inventions. Claim 26 is also withdrawn from consideration as being directed to a non-elected invention. In this regard the Office notes that while Applicant states in his traversal that claim 26 is cancelled, the listing of the claims submitted with Applicant's election indicates that original claim 26 is still pending. Accordingly claim 26 is withdrawn from consideration pending clarification of its status.

The requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

Initialed and dated copies of Applicant's IDS forms 1449, filed June 13, 2002 and June 18, 2002, are attached to the instant Office action.

Claim Objections

Claim 16 is objected to because of the following informalities: the claims recite non-elected enzymes. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-18 and 20-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method for improving vanillin production in *Vanilla planifolia* by genetically engineering *Vanilla planifolia* to overproduce any enzyme associated with chain shortening of p-coumaric acid to p-hydroxybenzaldehyde, including any p-hydroxybenzaldehyde synthase, and further including a p-hydroxybenzaldehyde synthase comprising the amino acid sequence of SEQ ID NO:2 or any functional variant thereof. The claims are also drawn to a

genetically engineered *Vanilla planifolia* cell or plant, including a genetically engineered *Vanilla planifolia* cell which produces at least twice as much vanillin as a non-genetically engineered cell.

The specification describes a nucleic acid of SEQ ID NO:1 obtained from *Vanilla planifolia* that encodes a p-hydroxybenzaldehyde synthase of SEQ ID NO:2, and suggests that this nucleic acid may be used to genetically engineer *Vanilla planifolia* in order to improve vanillin production (sequence listing; page 6 line 6 to page 7 line 3). The specification does not describe functional variants of the p-hydroxybenzaldehyde synthase comprising SEQ ID NO:2, or other p-hydroxybenzaldehyde synthase enzymes, or other enzymes associated with chain shortening of p-coumaric acid to p-hydroxybenzaldehyde.

The Federal Circuit has recently clarified the application of the written description requirement. The court stated that "A description of a genus of cDNAs may be achieved by means of recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." See *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1569; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In the instant case Applicant has not described a representative number of species falling within the scope of the genus of sequences to be used to genetically engineer *Vanilla planifolia* to overproduce an enzyme associated with chain shortening of p-coumaric acid to p-hydroxybenzaldehyde, or the genus of sequences to be used to genetically engineer *Vanilla planifolia* to overproduce p-hydroxybenzaldehyde synthase enzymes, or the genus of sequences to be used to genetically engineer *Vanilla planifolia* to overproduce functional variants of the p-

hydroxybenzaldehyde synthase comprising SEQ ID NO:2. Furthermore, Applicant has not described the structural features unique to any of these genera. Absent a description of the sequences to be used, the claimed methods directed to the use of such sequences, and the claimed products that comprise such sequences, are not adequately described.

Claims 16-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to a method for improving vanillin production in *Vanilla planifolia* by genetically engineering in any manner *Vanilla planifolia* to overproduce any enzyme associated with chain shortening of p-coumaric acid to p-hydroxybenzaldehyde obtained from any source, including any p-hydroxybenzaldehyde synthase and a p-hydroxybenzaldehyde synthase comprising the amino acid sequence of SEQ ID NO:2 or any functional variant thereof, and further including a p-hydroxybenzaldehyde synthase encoded by SEQ ID NO:1. The claims are also drawn to a genetically engineered *Vanilla planifolia* cell or plant, including a genetically engineered *Vanilla planifolia* cell which produces at least twice as much vanillin as a non-genetically engineered cell.

The specification discloses that a nucleic acid of SEQ ID NO:1 encoding a 4-hydroxybenzaldehyde synthase of SEQ ID NO:2 was obtained from a *Vanilla planifolia* embryo culture cDNA library by PCR amplification (page 60 lines 17-23; page 77 to page 79 line 24). The specification also discloses that the nucleic acid of SEQ ID NO:1 was used to transform

bacteria and yeast, and that yeast transformants were selected by their ability to uptake coumaric acid substrate from the culture media, followed by evaluation of extracts for formation of p-hydroxybenzaldehyde product (page 60 line 24 to page 61 line 18; page 80 line 1 to page 81 line 22; Figures 4 and 5). The specification further discloses that the nucleic acid of SEQ ID NO:1 was used to transform *Arabidopsis* and creeping bentgrass (page 99 lines 1-23; page 102 line 5 to page 104 line 17). The specification does not disclose the transformation of *Vanilla planifolia* with the nucleic acid of SEQ ID NO:1, or the effect of expressing its encoded polypeptide on the production of vanillin in any cellular or organismal system. The specification also does not disclose functional variants of the p-hydroxybenzaldehyde synthase comprising SEQ ID NO:2, or other p-hydroxybenzaldehyde synthase enzymes, or other enzymes associated with chain shortening of p-coumaric acid to p-hydroxybenzaldehyde.

The disclosure is not enabling for the claimed invention because it does not provide sufficient guidance for one skilled in the art to determine how to overproduce an enzyme associated with a chain shortening of p-coumaric acid to p-hydroxybenzaldehyde, such as the p-hydroxybenzaldehyde synthase of SEQ ID NO:2, in a manner that would improve the production of vanillin in *Vanilla planifolia*, or in a manner that would produce a *Vanilla planifolia* cell which produces at least twice as much vanillin as a non-genetically engineered cell. Such guidance is necessary because it is unpredictable whether the overproduction of an enzyme associated with chain shortening of p-coumaric acid to p-hydroxybenzaldehyde would improve the production of vanillin in *Vanilla planifolia*, as the chain shortening of p-coumaric acid to p-hydroxybenzaldehyde is but one of several steps required for vanillin biosynthesis. Improvement of the production of vanillin in *Vanilla planifolia* cells by overexpression of p-

hydroxybenzaldehyde synthase would depend not only upon the availability of sufficient p-coumaric acid substrate for the enzyme, but also on the downstream activity of other enzymes required to covert p-hydroxybenzaldehyde product into vanillin, as well as the activity of catabolic enzymes.

See for example, Havkin-Frenkel et al. (Food Technology, 1997, 51(11), 56-58, 61, Applicant's IDS) who teach that roughly 80% of coumaric acid applied to cultured *Vanilla planifolia* in feeding experiments was recovered as p-hydroxybenzyl alcohol (HBA) , whereas feeding of pro-aldehyde (3,4-dihydroxybenzaldehyde), produced by hydroxylation of p-hydroxybenzyl alcohol (HBA), led to the accumulation of vanillin (page 57 column 1 first full paragraph to column 2 first paragraph). Havkin-Frenkel et al. also concluded that the hydroxylation of p-hydroxybenzyl alcohol (HBA) to pro-aldehyde (3,4-dihydroxybenzaldehyde) is a limiting step in the vanillin biosynthetic pathway (page 57 column 1 second full paragraph to column 2 first paragraph). See also Applicant's own disclosure, which teaches that the activity of more than one enzyme is required for the biosynthesis of vanillin (Figure 1), that the hydroxylation of p-hydroxybenzyl alcohol to 3,4-dihydroxybenzaldehyde (proaldehyde) by a cytochrome P450 monooxygenase is believed to be the rate limiting step in vanillin biosynthesis (page 15 lines 2-6; page 16 lines 6-9), that the conversion of 4-coumaric acid to 4-hydroxybenzaldehyde is not considered to be the rate-limiting step in vanillin biosynthesis in cultured cells (page 20 lines 6-11), and that in cultured cells much of the vanillin produced is reduced to vanillyl alcohol, which depletes the culture of accumulated vanillin (page 15 lines 10-13).

Given that multiple variables affect the production of vanillin in *Vanilla planifolia*, and given the lack of guidance in the disclosure and in the prior art, it would require undue experimentation for one skilled in the art to determine how to overproduce an enzyme associated with a chain shortening of p-coumaric acid to p-hydroxybenzaldehyde in a manner that would improve the production of vanillin in *Vanilla planifolia*, or in a manner that would produce a *Vanilla planifolia* cell which produces at least twice as much vanillin as a non-genetically engineered cell, as one skilled in the art would have to resort to trial and error experimentation in order to optimize, if possible, multiple variables in order to achieve the desired results.

The disclosure also is not enabling for the claimed invention because it does not provide sufficient guidance for one skilled in the art to determine how to genetically engineer *Vanilla planifolia* to overproduce enzymes associated with chain shortening of p-coumaric acid to p-hydroxybenzaldehyde, other than by transformation with a nucleic acid encoding the p-hydroxybenzaldehyde synthase of SEQ ID NO:2. While the claims are directed to methods of genetically engineering *Vanilla planifolia* by any undefined means such that the engineered plant overproduces any enzyme associated with chain shortening of p-coumaric acid to p-hydroxybenzaldehyde, including any p-hydroxybenzaldehyde synthase, the specification only provides guidance for one means of genetically engineering *Vanilla planifolia* to overproduce only one enzyme associated with chain shortening of p-coumaric acid to p-hydroxybenzaldehyde, namely transformation with a nucleic acid encoding the p-hydroxybenzaldehyde synthase of SEQ ID NO:2. The specification does not provide guidance with respect to how to achieve this result with other methods of genetic engineering, such as breeding, for example. The specification also does not provide guidance with respect to how to

achieve this result using other nucleic acids, such as nucleic acids that encode proteins that regulate the expression of p-hydroxybenzaldehyde synthase, or nucleic acids that encode other enzymes associated with chain shortening of p-coumaric acid to p-hydroxybenzaldehyde, or other p-hydroxybenzaldehyde synthases obtained from other organisms. Such guidance is necessary because one skilled in the art needs access to the materials necessary to practice the claimed invention, and such materials do not appear to be accessible in the prior art. Neither the prior art of record nor the disclosure indicate the source of other sequences, or parental plant lines, that one skilled in the art could use to practice the claimed invention. Additionally, Applicant's own disclosure asserts that the data provided in the specification provide the first example of the molecular characterization of a plant chain-shortening enzyme (page 86 lines 11-13).

Given that the rejected claims encompass the use of any and all methods of genetically engineering *Vanilla planifolia* to overproduce any and all enzymes associated with a chain shortening of p-coumaric acid to p-hydroxybenzaldehyde, and given the lack of guidance in the disclosure and in the prior art, it would require undue experimentation for one skilled in the art to determine which enzymes to overproduce, and how to genetically engineer *Vanilla planifolia* to overproduce them, as one skilled in the art would have to resort to trial and error experimentation in order to identify and clone the genes for the desired enzymes, and/or to identify parental plant lines that could be crossed to produce *Vanilla planifolia* plants having the desired traits.

Remarks

No claim is allowed.

Claims 16-25 are deemed free of the prior art, due to the failure of the prior art to teach or suggest genetically engineering Vanilla planifolia to overproduce an enzyme associated with chain shortening of p-coumaric acid to p-hydroxybenzaldehyde, or a nucleic acid encoding the p-hydroxybenzaldehyde synthase of SEQ ID NO:2.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia Collins whose telephone number is (571) 272-0794. The examiner can normally be reached on Monday-Friday 8:45 AM -5:15 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Cynthia Collins  4/30/04